JACC Vol. 15, No. 4
March 15, 1990:763–74

SEMINAR ON SMALL CORONARY ARTERY DISEASE: STRUCTURE AND FUNCTION OF SMALL CORONARY ARTERIES IN HEALTH AND DISEASE—II*

Thomas N. James, MD, FACC, Albert V. G. Bruschke, MD, FACC, *Guest Editors*

The Spectrum of Diseases of Small Coronary Arteries and Their Physiologic Consequences

THOMAS N. JAMES, MD, FACC

There is a wide spectrum of abnormalities in the structure of small coronary arteries, with regard both to the portion of the arterial wall involved and to the histologic nature of the disease. A fuller understanding of this spectrum permits more useful interpretation of the pathophysiologic basis for the functional consequences of small coronary artery disease.

In this review based on personal observations during examination of more than 1,000 human hearts postmortem there is initially a description of the wide variety of structural abnormalities, then a discussion of the functional consequences of these abnormalities and finally a section of general comments to weave together the structural and functional discussion in the context of clinical evaluation of patients who have small coronary artery disease. Future studies should apply fractal analysis and quantitative topology, methods that lend themselves particularly well to an investigation of the progressively smaller branching of the human coronary tree.

(J Am Coll Cardiol 1990;15:763–74)

Structural abnormalities of small coronary arteries differ histologically not only from one disease to another, or from one section of the heart to another in a patient with the same disease, but even from one segment of a small coronary artery to another in the same artery. It is important to understand this wide variety of histologic lesions and their potentially different functional significance in order best to interpret their clinical manifestations. For example, for the pathogenesis of spasm, or the possible effect on longitudinal propagation of contraction in the wall of a coronary artery (1) or the conduction serially down a line of smooth muscle cells of the tunica media (2), different types of lesions may have very different functional effects. In reactive hyperemia, relatively normal smooth muscle cells are required and coordination of their response along the vessel is important, but some diseases of small coronary arteries not only damage but may completely replace the tunica media with scar or infiltrate it with an abnormal substance such as amyloid.

Methods of Study

The purpose of this review is to describe the spectrum of abnormalities that can be found in the small coronary arteries of the human heart (arbitrarily those with an external diameter of 0.1 to 1.0 mm), and to discuss the functional consequences that many of them share but some of them uniquely introduce. The source of observations is my own experience in the past 30 years during which I have personally examined more than 1,000 human hearts by gross dissection followed by histologic study. The hearts have come principally from autopsy of persons who died suddenly and unexpectedly or from patients with recently documented arrhythmias or conduction disturbances, particularly if the underlying disease was one with readily defined histologic features (such as hemochromatosis or thrombotic thrombocytopenic purpura).

Methods for these studies in my laboratory have been

*Part I of this Seminar appeared in the March 1, 1990 issue of the Journal.

From the Department of Medicine and the Department of Pathology, University of Texas Medical Branch, Galveston, Texas. This work was supported in part by the Pegasus Fund of the University of Texas Medical Branch, Galveston, Texas.

Manuscript received September 23, 1989, accepted October 9, 1989.

Address for reprints: Thomas N. James, MD, Office of the President, University of Texas Medical Branch, Galveston, Texas 77550-2774.

0735-1097/90/$3.50

JACC Vol. 15, No. 4
March 15, 1990:763–74

previously published (3,4) but for this review may be briefly summarized as follows. Particular attention is routinely directed to all elements of the cardiac conduction system, including its blood supply. One special block containing the sinus node and another the atrioventricular (AV) node and His bundle with its branches are routinely removed, sliced serially at about 2 mm intervals and then at least 10 serial sections about 8 μm thick are mounted, stained and studied from each slice. For the sinus node several centimeters of adjacent right atrial free wall and of sinus intercavarum are routinely included, and for the AV junctional tissues at least 2 cm of both atrial and ventricular septa are included. This extra tissue always provides samples of atrial and ventricular arteries as well as of those especially supplying the conduction system. In most hearts still more tissue from the free walls of ventricular and atrial myocardium is also examined. In an average study several hundred different profiles of small coronary arteries are examined per heart.

From this cumulative experience the subject of the structure and function of small coronary arteries will be discussed on the basis of two effects: processes or events that *obstruct* the lumen of the vessel and abnormalities that *impair vasomotion* (particularly vasoconstriction or vasodilation, or both). Of course, these two functional faults are not easily separated. For example, focal fibromuscular dysplasia thickens the wall and narrows the lumen, but it may either enhance or impair constriction and almost certainly impairs dilation. Other overlapping abnormalities having multiple effects will similarly require special consideration.

Luminal Obstruction

Thrombosis. For large coronary arteries thrombosis is not unusual and has major clinical consequences. In small coronary arteries isolated thrombosis in situ (that is, without local endothelial disease) is much less frequently seen but may occur and can have important consequences, as when it occludes the sinus node artery (5). Two forms of hematogenous luminal obstruction include embolic debris of various sorts (6) and the generalized clotting disorders characteristic of thrombotic thrombocytopenic purpura (7) and disseminated intravascular coagulation (8).

Detritemia. Blood-borne debris may embolize into the small coronary arteries under at least two conditions. Assorted particles may embolize during or after cardiac surgery (13–17) and from either the mitral or the aortic valve in patients with diseases such as bacterial endocarditis or rheumatic valvulitis (Fig. 1) (9–12). A more recent problem is microembolization associated with percutaneous transluminal angioplasty (18,19). The clinical consequences depend on the number of such emboli and where they lodge within the heart. If there are many such emboli, they may account for the intractable low output failure sometimes encountered after cardiac surgery. If the emboli occlude special arteries such as those supplying the conduction system, then electrical instability and even sudden death may result. Other diseases that may also influence the heart in a similar fashion include air embolism (20), fat embolism (21), certain tumor metastases (22) and advanced septic conditions.

Endothelial lesions. Any pathologic process that alters endothelial structure can lead to two luminal obstructing effects: cellular proliferation involving endothelium and other components of the tunica intima, and an enhanced tendency to local thrombosis. A paradigm of such effects is congenital homocystinuria (23). Homocystine has a direct injurious effect on endothelium that is manifested at many sites by intimal proliferation sometimes including smooth muscle in a dysplastic array (Fig. 2). These reactive endothelial lesions may attract platelet aggregations that already are favored by the known generalized aggregating tendency of platelets in such patients (24–26). Intimal injury and platelet aggregation affect all vessels in patients with congenital homocystinuria, including large arteries and veins as well as the small coronary arteries.

Arteritis. One consequence of arteritis also can be luminal obstruction of small coronary arteries. That caused by polyarteritis (Fig. 3) (27) or lupus erythematosus (28) is purely inflammatory, but that occurring in Whipple's disease includes intramural and endothelial infection as well as inflammation (29,30). Surprisingly, mural invasion by the Whipple's disease bacillus is devoid of inflammation at some sites, yet causes typical arteritis at other sites even in the same heart. With arteritis that is purely or primarily adventitial, the endothelium is spared and local thrombosis less likely. But when the endothelium is involved, as in panarteritis of any etiology, local platelet aggregation and thrombosis add to the luminal narrowing consequences.

Mural thickening. Some diseases narrow the lumen of small coronary arteries but seldom lead to thrombosis or even much involvement of the tunica intima. Examples include focal fibromuscular dysplasia (31–33), amyloidosis (34) and the intramural deposit of Schiff-positive material characteristic of small coronary arteries in the cardiomyopathy of Friedreich's ataxia (Fig. 4) (35,36). Focal fibromuscular dysplasia may be idiopathic or at least of currently unknown cause, but it is also prominently seen in patients with several different cardiomyopathies such as scleroderma heart disease (37) and idiopathic cardiomyopathy (38). Focal fibromuscular dysplasia may be sufficiently extensive to close the lumen of a small coronary artery, but even lesser degrees can significantly narrow the lumen, an effect that may then be compounded by local spasm (39,40). The synergistic combination of medial thickening and local spasm will be further discussed in the section on vasomotion.

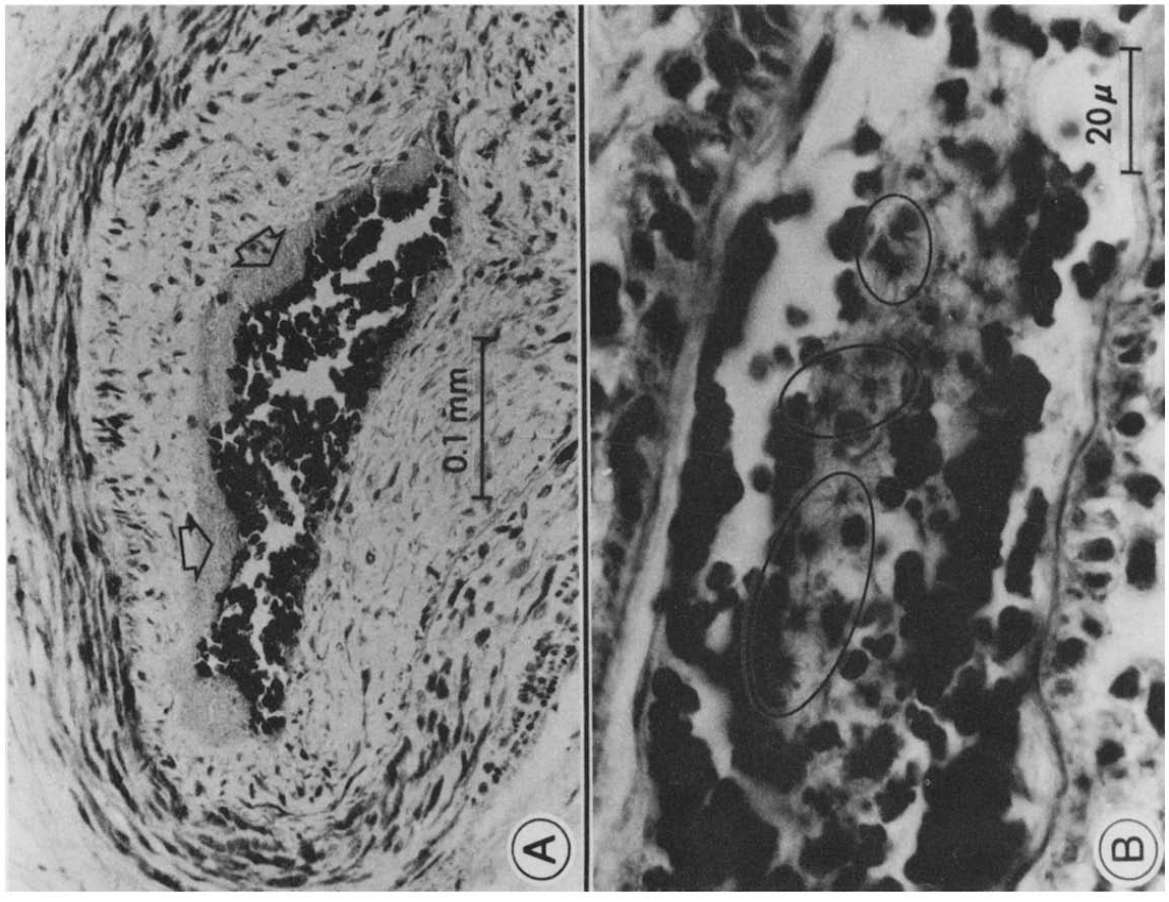


Figure 2. Two photomicrographs from the heart of a boy who died of congenital homocystinuria and a recent myocardial infarction. The small artery in **A** is in the AV node and exhibits both medial and myointimal dysplasia as well as a layer of aggregating platelets (two open arrows). Several star-shaped clusters of aggregating platelets within the lumen of the sinus node artery are encircled in **B**.

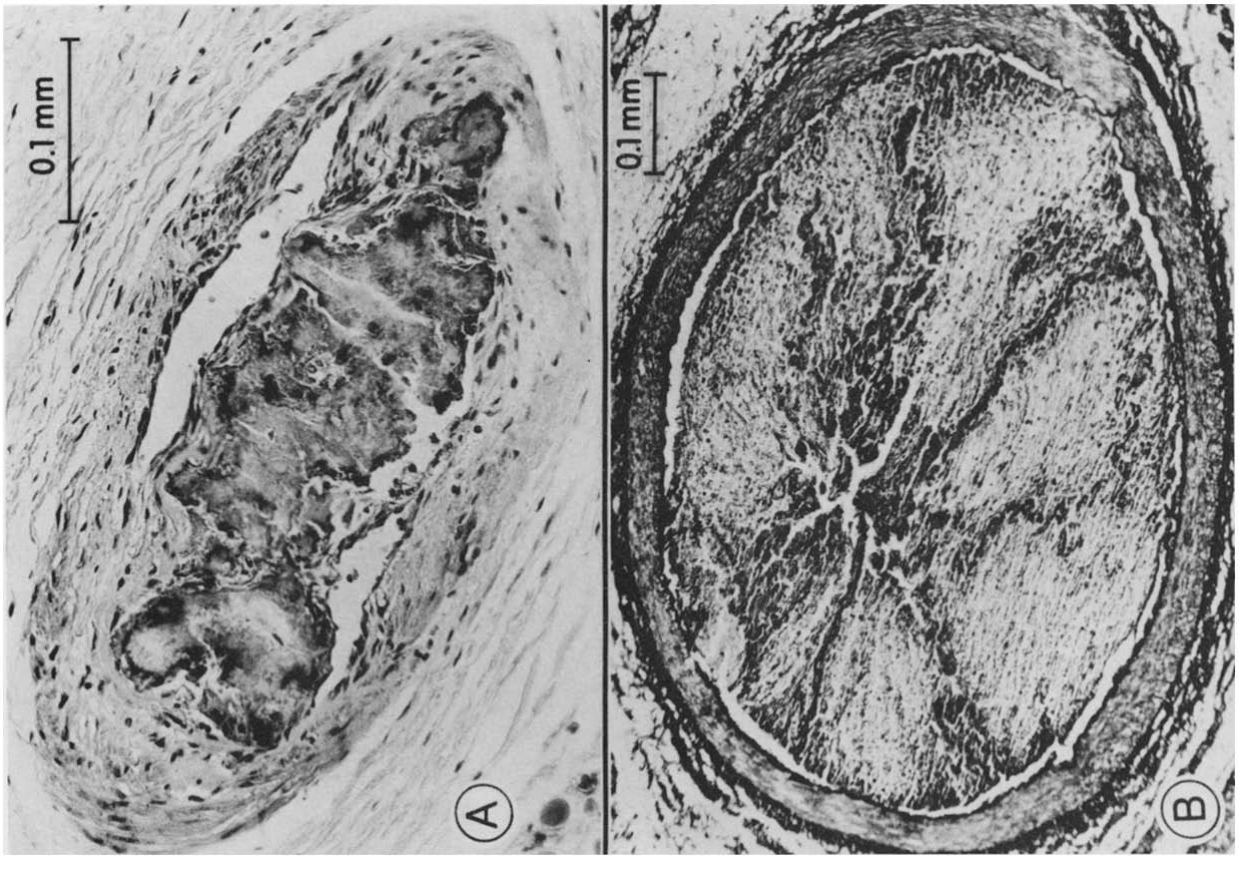


Figure 1. Examples of embolic debris occluding small coronary arteries. The coarse fragment in **A** was found in a small ventricular septal artery in the heart of a young man who died shortly after replacement of his aortic valve. The embolic clot in **B** (Verhoeff-van Gieson elastic stain) occluded the sinus node artery of a young woman who died of rheumatic mitral stenosis and atrial fibrillation. The stain in **A** and in all other illustrations (unless otherwise indicated) is the Goldner trichrome stain. All magnifications are indicated with reference bars.

JACC Vol. 15, No. 4
March 15, 1990:763–74

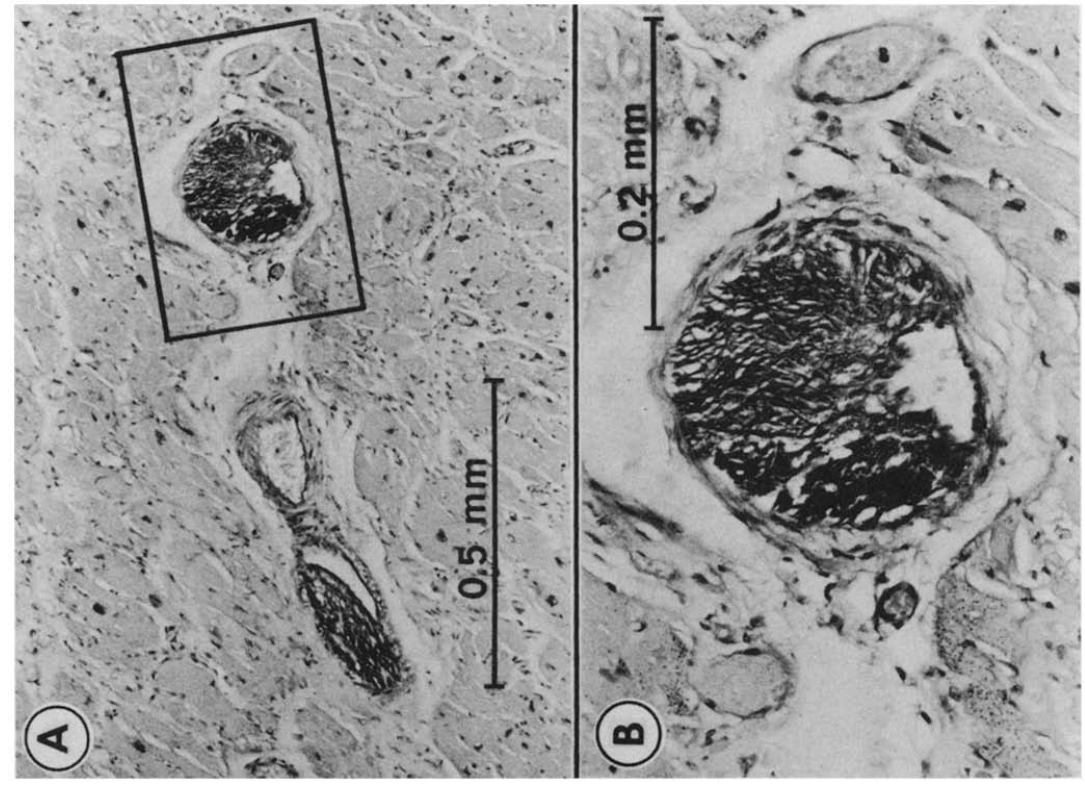


Figure 4. An unusual Schiff-positive material infiltrates the wall of small coronary arteries in the cardiomyopathy of Friedreich's ataxia as shown here from the heart of a young man who died of such cardiomyopathy. Area boxed in A is from the free wall of the left ventricle and is seen at higher magnification in B. Periodic acid-Schiff stain.

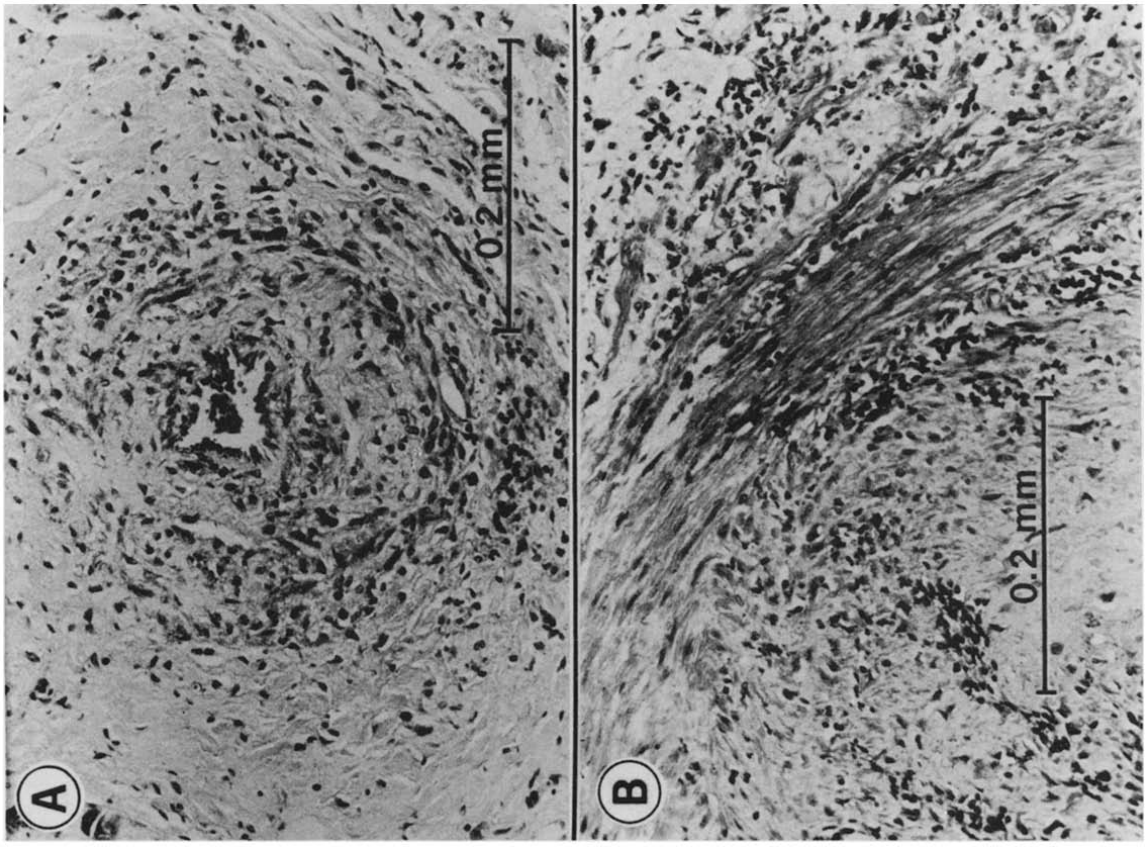


Figure 3. Panarteritis of small coronary arteries from the heart of two different individuals who died of polyarteritis nodosa. A, From the sinus node; B, From the AV node.

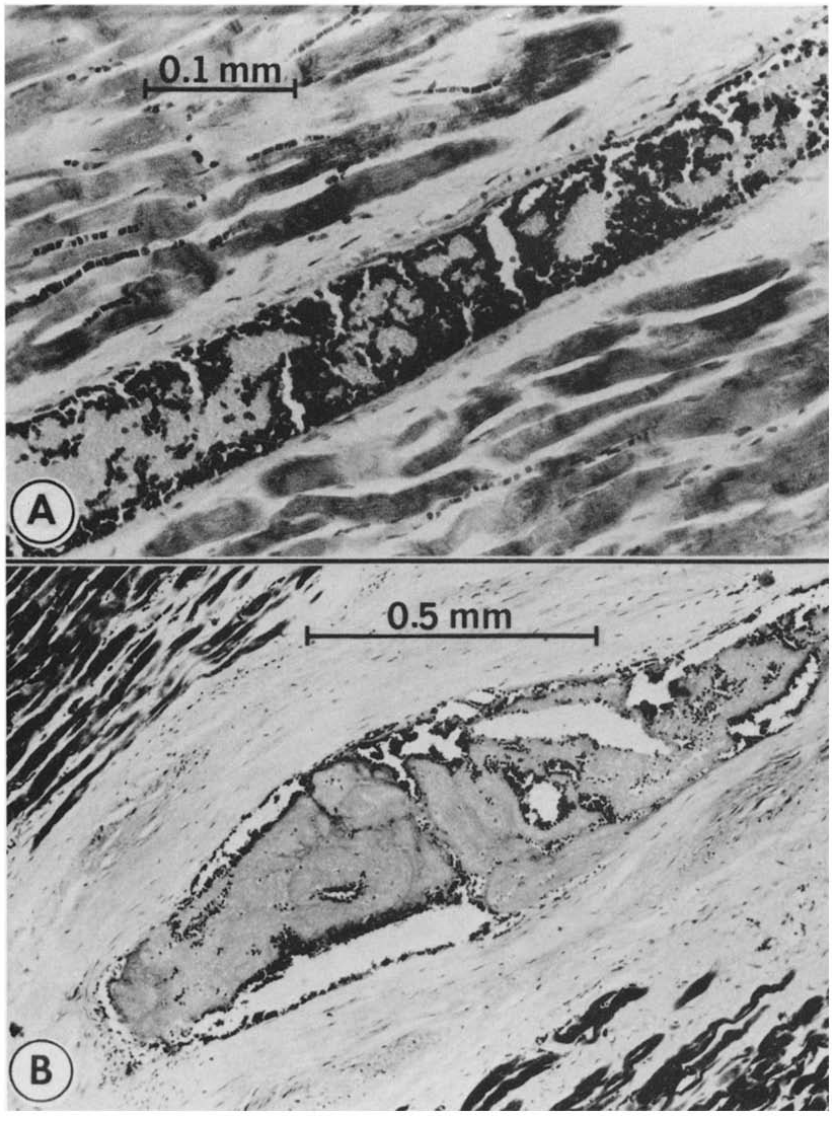


Figure 5. Platelets aggregate within the lumen of small coronary arteries in victims of fatal pheochromocytoma, as shown from the heart of an older woman. **A,** Platelets are clumped within the lumen of a left ventricular artery cut longitudinally. **B,** An older platelet aggregation is adherent to the endothelium.

Impaired Vasomotion

Constriction and dilation. Metabolic needs of the myocardium depend on normal and appropriate vasoconstriction or dilation of small coronary arteries during a variety of stressful challenges. If a small artery cannot dilate, normal responses such as reactive hyperemia cannot occur. Although less is known of the circumstances normally requiring constriction of small coronary arteries, it may reasonably be assumed that physiologic vasoconstriction must intermittently occur in the heart as in all other areas of the body.

For most of the diseases being discussed, the walls of small coronary arteries may be stiffened, with or without much direct luminal encroachment, and with all of them the local response to vasoactive agents, whether normally circulating in the blood or released by nerve endings or whether administered in therapy, will almost certainly be altered, sometimes enhancing and sometimes negating the vasoactive effect. When the wall of a small coronary artery is weakened, as in any form of medial degeneration or destruction, the vessel may locally dilate (actually, be distended by normal intravascular pressure) but would otherwise be unlikely to respond to usual vasoactive influences.

Longitudinal propagation of contraction. Recent studies have demonstrated a highly organized longitudinal contraction of coronary arteries from human hearts (1), a process that presumably includes the need for calcium-dependent electrical conduction between involved cells (2). Any of a variety of the lesions being discussed could play havoc with this orderly process. Although one can only conjecture about the functional significance of disrupted longitudinal propagation of contraction in coronary arteries, it seems highly likely that vasomotion would become impaired and that eddy currents or abnormal turbulence could occur. In this context, it is of some interest that hydraulic engineers conducting in vitro tests of flow by non-Newtonian fluids in tubes have demonstrated that the introduction of appropriate

JACC Vol. 15, No. 4
March 15, 1990:763–74

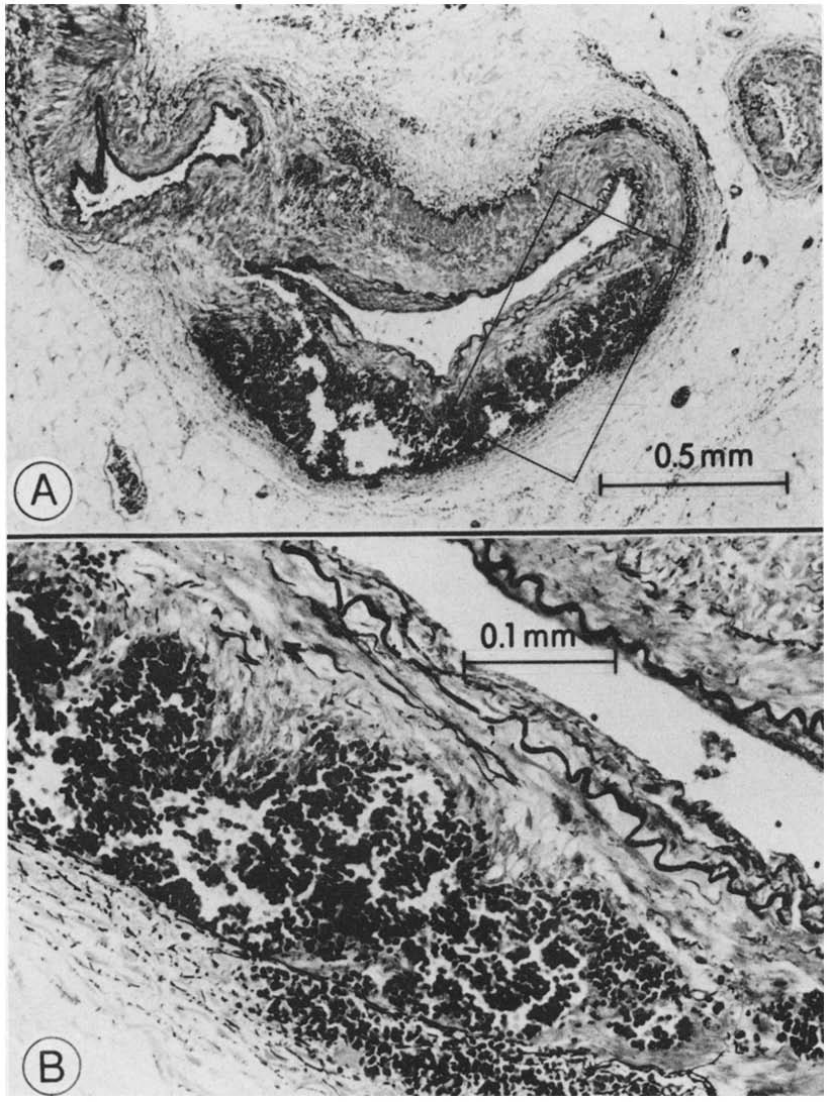


Figure 6. Mural dissection of the sinus node artery from the heart of an older woman with fatal hepatic cirrhosis. Area boxed in A is seen at higher magnification in B. Verhoeff-van Gieson elastic stain.

baffles or other specially arranged partial obstructions could cause sufficient turbulence so that forward flow would cease or reverse even when the actual tubular lumen remained patent (41).

Complex relations between diseases and vasomotion. Until recently it was generally believed that vasomotion was virtually entirely dependent on the activity of the tunica media. However, one of the more important new concepts in vascular biology is the growing recognition of the importance of the endothelium in both the constricting and the dilating activity of arteries (42–45). An intact endothelium not only regulates the effects of many vasoactive humoral substances, which it may or may not allow to pass either intact or metabolically modified, but endothelial cells also provide vasoactive substances themselves. In the preceding section certain diseases affecting the tunica intima and endothelial cells of small coronary arteries were reviewed, such as the arteritides and congenital homocystinuria. To these may be added pheochromocytoma, which may have a direct constricting effect on small coronary arteries but also causes widespread platelet aggregation (Fig. 5) in the small arteries both in the lungs and in the heart, and at each site furthermore causes scattered foci of endothelial proliferation (46). All three effects (platelet aggregation, endothelial proliferation and spasm) not only significantly narrow the lumen but also distort local vasomotion of the vessel. These effects of increased levels of circulating catecholamines may lead to multifocal myocardial ischemia that is simultaneously and paradoxically combined with a positive inotropic effect (increased metabolic demand) to produce the so-called myocarditis (47) of pheochromocytoma.

Mural infiltration. Any disease that alters the structure and reactivity of the tunica media in small coronary arteries predictably will derange their vasomotion. Infiltration damages the tunica media in amyloidosis, which has multiple other effects as well, but a less familiar example is the Schiff-positive medial infiltration of small coronary arteries in the cardiomyopathy of Friedreich's ataxia (Fig. 4) (35,36).

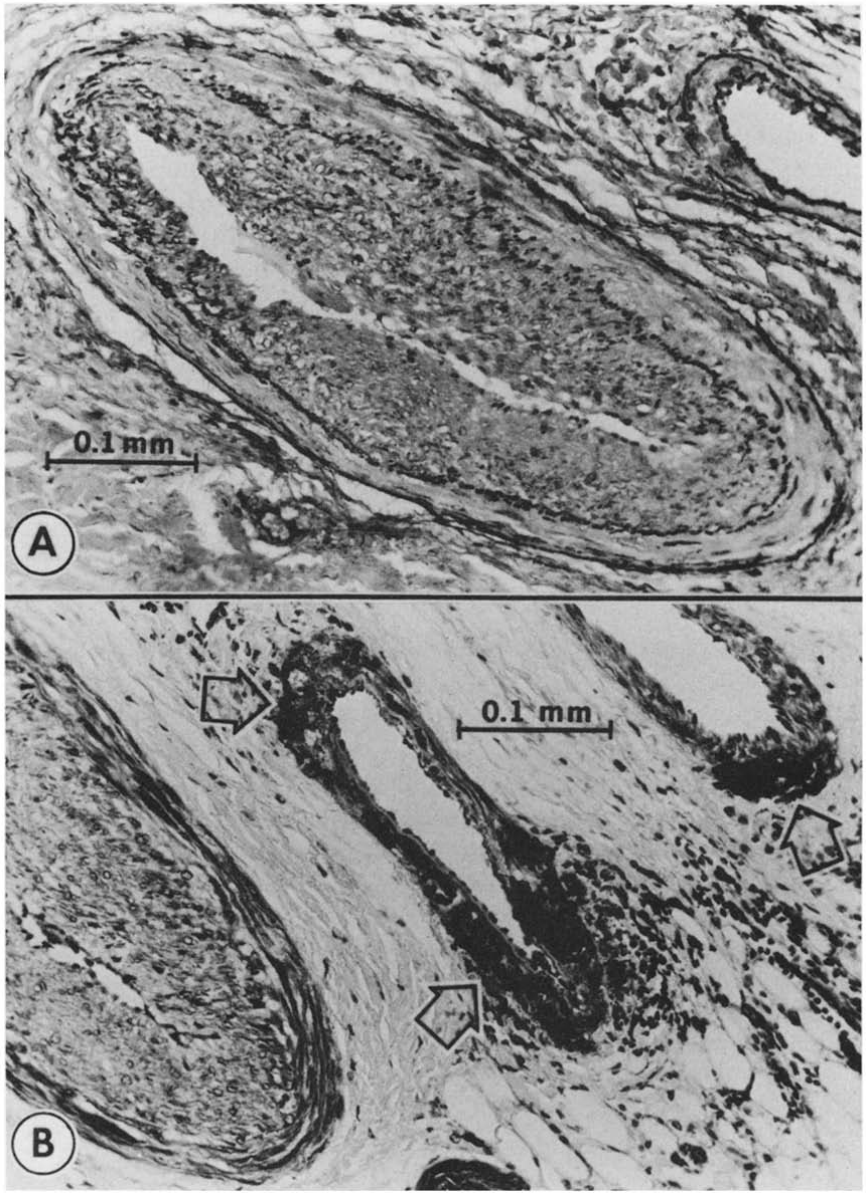


Figure 7. Branches of the AV node artery from the heart of a young man who died of Marfan's syndrome. A, the main AV node artery exhibits myointimal dysplasia narrowing its lumen (Verhoeff-van Gieson elastic stain) whereas in B one sees medial degeneration with mural hemorrhage (three open arrows) within two small branches of the AV node artery.

Medial fibrosis as seen in the healing phase of arteritis may be similarly considered.

Hereditary medial necrosis. Rarer forms of damage to the tunica media of small coronary arteries include local dissection (Fig. 6) (9) and the unusual medial hemorrhage and noninflammatory necrosis found in small coronary arteries of the hearts of persons dying of primary pulmonary hypertension (48,49), ordinarily considered almost exclusively a disease of the lungs. Similar but less extensive medial hemorrhage and necrosis occur in Marfan's syndrome (Fig. 7) (50). Medial necrosis with or without mural hemorrhage may also be found in the small coronary arteries of a variety of other heritable neuromuscular or musculoskeletal disorders (nonhypertensive) including progressive muscular dystrophy (51) and Friedreich's ataxia (35,36). Although the sites of such medial degeneration sometimes include cystic features, it is not a process in any other way resembling cystic degeneration of the aorta.

Inflammatory medial degeneration. Various arteritides may cause inflammatory destruction of the tunica media, in most cases later leading to medial fibrosis or focal fibromuscular dysplasia, or both, as the inflammation wanes. Whipple's disease (Fig. 8 and 9) (29,30), polyarteritis nodosa (27), rheumatoid arthritis (52) and lupus erythematosus (28) are all examples associated with arteritis of small coronary branches, and they all thus may impair vasomotion and thereby distort normal nutrient circulation to the myocardium.

Spasm. Any thickening of the tunica media can cause direct narrowing of the arterial lumen, but when the thick-

JACC Vol. 15, No. 4
March 15, 1990:763–74

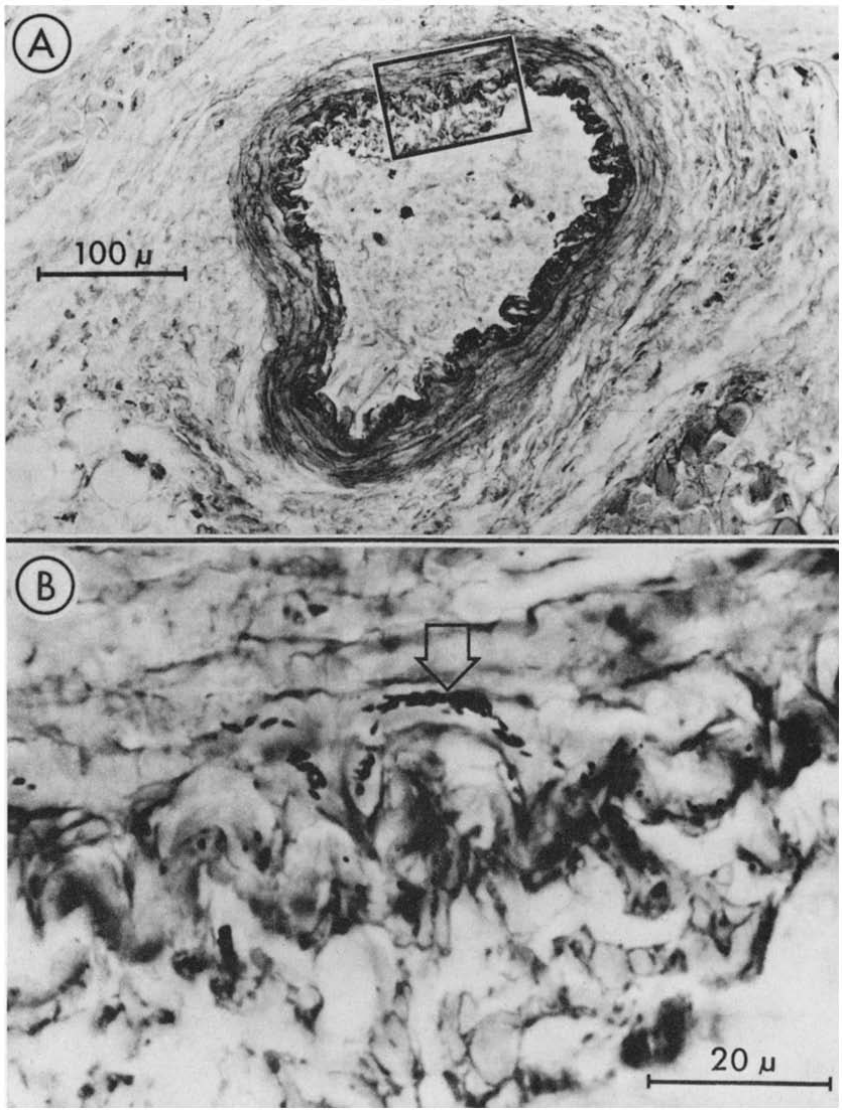


Figure 8. A, A small coronary artery from the interventricular septum of an older man who died of Whipple's disease (periodic acid-Schiff stain). B, The boxed area in A is seen at higher magnification where the Schiff-positive bacilli are clearly visible, one small group being indicated with an open arrow. Note the absence of any inflammatory response and compare with Figure 9, which is from the same heart.

ening is caused by increased smooth muscle mass, one must especially consider the compounding additional influence of spasm. Very little mural thickening is required for superimposed spasm to have a profound effect (39,40). For example, focal fibromuscular dysplasia (if it responds normally or even with enhanced vasoconstriction) of a degree that reduces the radius of the lumen by 30% requires only a 9% reduction in the external radius of the artery by spasm to cause an 80% decrease in the internal radius. For a small coronary artery with 50% narrowing of the radius of the lumen, still usually considered of marginal significance in itself, a mere 9% decrease of the external radius by spasm is all that is required to obliterate the lumen completely.

Special vasoactive responses. Among other emerging concepts of vasomotion, there is now evidence that neuropeptide Y (and possibly other substances) may have an almost selective effect in causing constriction of small coronary arteries (53), an observation of potential relevance to the pathogenesis of certain cardiomyopathies (54,55). There is also evidence that both dipyridamole (56) and uridine triphosphate (57) may have a selective dilating effect on small coronary arteries, an effect with particular influence on the coronary anastomoses and collateral circulation (57).

General Comments

Effects of sites, numbers and progression on lesions. The expected consequence when a small coronary artery becomes narrowed or its vasomotion is impaired depends on where the artery is located and what it supplies (Fig. 10). Obstruction of a sufficient number of small coronary arteries supplying the *working myocardium* causes focal ischemia and degeneration and fibrosis, and ultimately ventricular failure. For arteries supplying the *conduction system* the

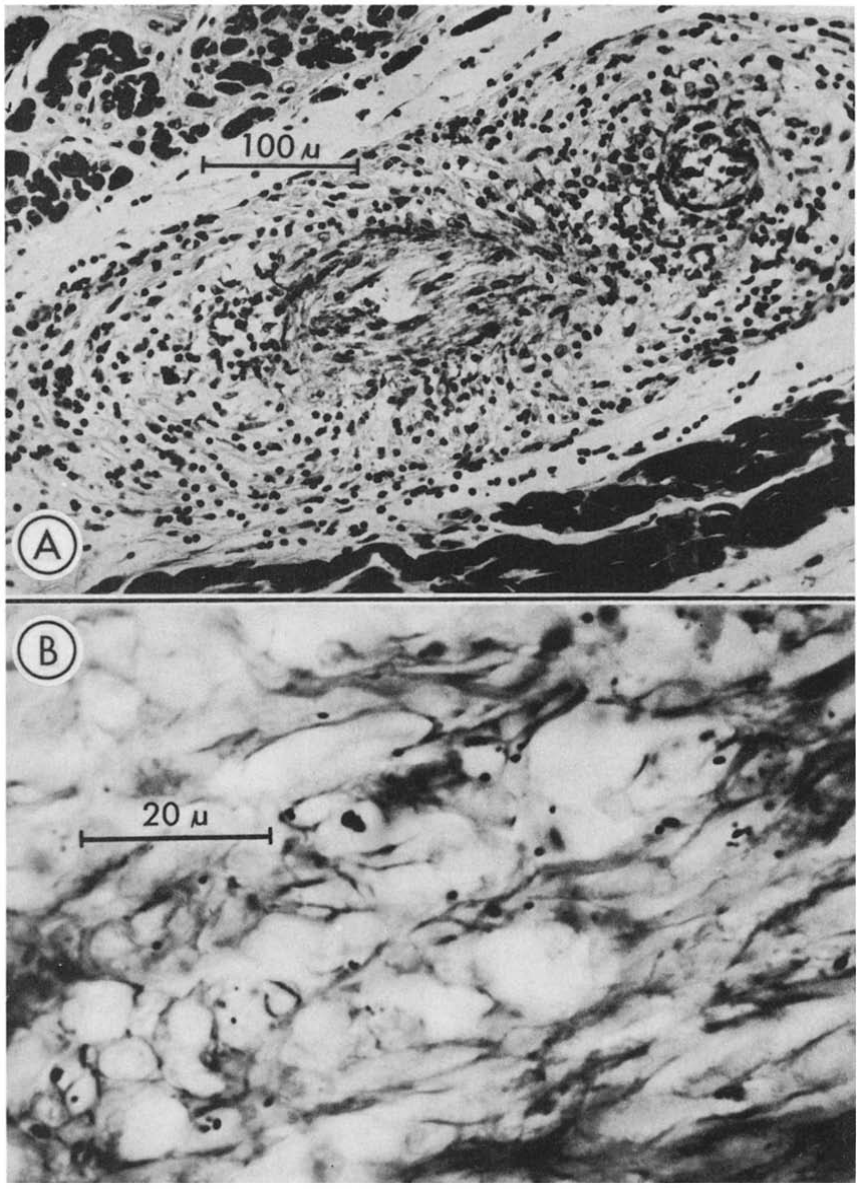
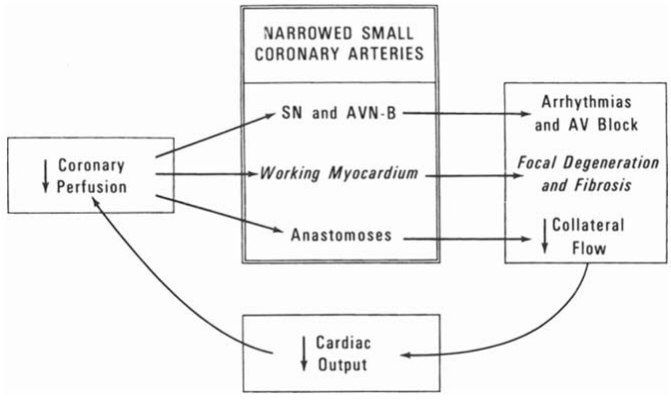


Figure 9. Same heart as in Figure 8. At some sites extensive inflammation accompanies mural infiltration of small coronary arteries by the Whipple bacillus. The examples shown here are from the left ventricular free wall. The section in A exhibits panarteritis whereas the one in B is a section adjacent to one in A but is stained with the periodic acid-Schiff method and is photographed at higher magnification. The Schiff-positive bacilli are scattered throughout the area in B, which is the same artery as in A.

result is electrical instability of the heart with arrhythmias, conduction disturbances and sudden death. For arteries forming the *intercoronary anastomoses* the result is impaired collateral circulation that compounds any of the other results and hastens the evolution of all forms of myocardial insufficiency. The speed with which multiple narrowing lesions develop and the final number of such sites also help determine the end result. Neither the site affected nor the speed of progression of lesions can be predicted at present, and lesions seem best considered as random events. In general terms, the usual clinical course of a disease such as amyloidosis or polyarteritis nodosa may also be taken as a crude indicator of what may be expected in its effect on small coronary arteries, keeping in mind the vexing nature of individual variation in response to any disease.

Figure 10. A diagrammatic depiction of the functional significance of small coronary disease. See text for discussion. AVN = atrioventricular node; SN = sinus node.



JACC Vol. 15, No. 4
March 15, 1990:763–74

Extracardiac and nonvascular intracardiac influences. Another confounding factor is the number of extracardiac and other intracardiac effects of many and perhaps all diseases affecting small coronary arteries. For example, amyloidosis definitely involves small coronary arteries (34) but it also involves the large ones, any of the cardiac valves and many intracardiac nerves and ganglia, and it destroys cardiac myocytes directly. Scleroderma narrows many small coronary arteries, but it may also cause either functional or structural abnormalities of the cardiac nerves and it seems to be associated with focal myocardial fibrosis of a greater degree than can be accounted for on the basis of its vascular lesions alone (37). Whipple's disease (29,30) may produce remarkable cardiac involvement including the small coronary arteries but may also cause pericarditis, valvulitis and granulomas that are distributed throughout the heart, in addition to its other important effects on the gastrointestinal and central nervous systems.

Different and similar effects of infiltrative diseases. Some infiltrative diseases have diametrically opposite effects on small coronary arteries. For example, both scleroderma and amyloidosis have an affinity for small coronary arteries, whereas hemochromatosis (58) conspicuously spares both large and small coronary arteries. But all three diseases cause infiltration and destruction of cardiac myocytes, including those in the conduction system.

Coronary reserve. Assessing precisely the effects produced by any disease of small coronary arteries in a given patient is difficult, although the measurement of coronary reserve (59–65) has become a useful clinical approach. Either luminal narrowing or impaired vasoreactivity of sufficient numbers of small coronary arteries may be expected to diminish the coronary reserve, albeit by different physiologic mechanisms. Knowledge of the diseases causing such changes will help in the interpretation of results from measuring coronary reserve. It is unsurprising, for example, that diminished coronary reserve has been demonstrated in the cardiomyopathy of Friedreich's ataxia (66) and in scleroderma heart disease. (67).

Three-dimensional nature of the coronary circulation. Whether attempting to explain the functional consequences of small coronary artery disease on the basis of measurement of coronary reserve, or from postmortem examination of many small coronary arteries, it is essential to remember that virtually every disease affecting these vessels is focal in nature and the foci are often as small as 1 mm in length. In postmortem histologic quantification it then becomes necessary to keep in mind the three-dimensional nature of the coronary tree, and that thin sections studied from a glass slide present only a two-dimensional picture. Many small coronary arteries are several centimeters in length whereas histologic sections are usually <10 μm thick. Calculations based on the chance encounter of significant narrowing lesions in small coronary arteries examined in histologic sections thus may be grossly underestimated as to their functional significance unless allowance is made for the length of such vessels, the small size of many hemodynamically important lesions and the small mathematical chance of encountering such lesions in a usual histologic slide examination.

Topology and fractal analysis. One new approach to the future quantification and assessment of small coronary disease may lie in thinking of physiology in fractal dimensions. Those examining novel uses of quantitative topology and fractal analysis of biologic phenomena frequently refer to the seeming randomness of the branching patterns of the tracheobronchial tree, the peripheral conduction system of the heart and the coronary circulation (68), emphasizing that what seems random actually exhibits a high order of organization following unusual but recognizable patterns of symmetry and asymmetry. There is growing interest by mathematicians, physicists and especially computer analysts in using these concepts to improve our understanding of many biologic questions and one may hope that the small coronary arteries will lend themselves to this imaginative new approach.

References

1. Araki H, Sakaino N, Furusho N, Nishi I. Longitudinal propagation of contraction in the isolated conduit coronary arteries of humans and pigs. Circ Res 1989;64:734–41.
2. Segal S, Duling BR. Flow control among microvessels coordinated by intercellular conduction. Science 1986;234:868–70.
3. James TN. Morphology of the human atrioventricular node, with remarks pertinent to its electrophysiology. Am Heart J 1961;62:756–71.
4. James TN. Anatomy of the human sinus node. Anat Rec 1961;141:109–39.
5. Winternitz M, Selye H. Ein Fall von Sinus Bradykardie durch Sinusarterienthrombose. Wien Arch Inn Med 1929;16:377–80.
6. Ingelfinger FJ. Detritemia. N Engl J Med 1975;292:696–7.
7. James TN, Monto RW. Pathology of the cardiac conduction system in thrombotic thrombocytopenic purpura. Ann Intern Med 1966;65:37–43.
8. James TN, Marshall ML, Craig MW. De Subitaneis Mortibus. VII. Disseminated intravascular coagulation and paroxysmal atrial tachycardia. Circulation 1974;50:395–401.
9. James TN. Pathology of small coronary arteries. Am J Cardiol 1967;20: 679–91.
10. Naeye RL, Liedtke AJ. Consequences of intramyocardial arterial lesions in aortic valvular stenosis. Am J Pathol 1976;85:569–80.
11. Oakley C, Yusuf R, Hollman A. Coronary embolism and angina in mitral stenosis. Br Heart J 1961;23:357.
12. Perry EL, Fleming RG, Edwards JE. Myocardial lesions in subacute bacterial endocarditis. Ann Intern Med 1952;36:126–37.
13. Morales AR, Fine G, Taber RE. Cardiac surgery and myocardial necrosis. Arch Pathol 1967;83:71–9.
14. Aboumrad MH, Gyorkey F. Two cases of coronary embolism following cardiac surgery. Arch Pathol 1969;88:547–8.
15. Patterson RH Jr, Kessler J. Microemboli during cardiopulmonary bypass detected by ultrasound. Surg Gynecol Obstet 1969;129:505–10.

16. Patterson RH Jr, Twichell JB. Disposable filter for microemboli. JAMA 1971;215:76–80.

17. Hearse DJ, Erol C, Robinson LA, Maxwell MP, Braimbridge MV. Particle-induced coronary vasoconstriction during cardioplegic infusion: characterization and possible mechanisms. J Thorac Cardiovasc Surg 1985;89:428–38.

18. Fischell TA, Derby G, Tse TM, Stadius ML. Coronary artery vasoconstriction routinely occurs after percutaneous transluminal coronary angioplasty: a quantitative arteriographic analysis. Circulation 1988;78: 1323–34.

19. Wilson RF, Lesser JR, Laxson, White CW. Intense microvascular constriction after angioplasty of acute thrombotic coronary arterial lesions. Lancet 1989;4:807–11.

20. James TN, Geoghegan T, Lam CR. Electrocardiographic manifestations of air in the coronary arteries of dying and resuscitated hearts. Am Heart J 1953;46:215–28.

21. Chester EM, Banker BQ. The role of lipid thrombi in the pathogenesis of diabetic retinopathy. Arch Intern Med 1967;120:397–407.

22. Lasky II. Fatal coronary artery tumor metastasis. Am Heart J 1984;107: 785–7.

23. James TN, Carson NAJ, Froggatt P. De Subitaneis Mortibus. IV. Coronary vessels and conduction system in homocystinuria. Circulation 1974;49:367–74.

24. Harker LA, Slichter SJ, Scott CR, Ross R. Homocystinema: vascular injury and arterial thrombosis. N Engl J Med 1974;291:537–43.

25. Harker LA, Ross R, Slichter SJ, Scott CR. Homocystine-induced arteriosclerosis: the role of endothelial cell injury and platelet response in its genesis. J Clin Invest 1976;58:731–41.

26. Mudd SH. Vascular disease and homocysteine metabolism. N Engl J Med 1985;313:751–3.

27. James TN, Birk RE. Pathology of the cardiac conduction system in polyarteritis nodosa. Arch Intern Med 1966;177:561–7.

28. James TN, Rupe CE, Monto RW. Pathology of the cardiac conduction system in systemic lupus erythematosus. Ann Intern Med 1965;63:402–10.

29. James TN, Haubrich WS. De Subitaneis Mortibus. XIV. Bacterial arteritis in Whipple's disease. Circulation 1975;52:722–31.

30. James TN, Bulkley BH. Abnormalities of the coronary arteries in Whipple's disease. Am Heart J 1983;105:481–91.

31. James TN, Froggatt P, Marshall TK. Sudden death in young athletes. Ann Intern Med 1967;67:1013–21.

32. James TN, Hackel DB, Marshall TK. De Subitaneis Mortibus. V. Occluded A-V node artery. Circulation 1974;49:772–7.

33. James TN, Marshall TK. De Subitaneis Mortibus. XVII. Multifocal stenoses due to fibromuscular dysplasia of the sinus node artery. Circulation 1976;53:736–42.

34. James TN. Pathology of the cardiac conduction system in amyloidosis. Ann Intern Med 1966;65:28–36.

35. James TN, Fisch C. Observations on the cardiovascular involvement in Friedreich's ataxia. Am Heart J 1963;66:164–75.

36. James TN, Cobbs BW, Coghlan HC, McCoy WC, Fisch C. Coronary disease, cardioneuropathy, and conduction system abnormalities in the cardiomyopathy of Friedreich's ataxia. Br Heart J 1987;57:446–57.

37. James TN. De Subitaneis Mortibus. VIII. Coronary arteries and conduction system in scleroderma heart disease. Circulation 1974;50:844–56.

38. James TN, Marshall TK. De Subitaneis Mortibus. XII. Asymmetrical hypertrophy of the heart. Circulation 1975;51:1149–66.

39. Van Citters RL. Occlusion of lumina in small arterioles during vasoconstriction. Circ Res 1966;18:199–204.

40. MacAlpin RN. Contribution of dynamic vascular wall thickening to luminal narrowing during coronary arterial constriction. Circulation 1980; 61:296–301.

41. Davis RF. Hemodynamics of the coronary circulation. In: Osborne GR. The Incubation Period of Coronary Thrombosis. London: Butterworths, 1963:144–54.

42. Furchgott RF. Role of endothelium in responses of vascular smooth muscle. Circ Res 1983;53:557–73.

43. Kaiser L, Sparks HV Jr. Endothelial cells: not just a cellophane wrapper. Arch Intern Med 1987;147:569–73.

44. Vanhoutte PM. The endothelium: modulator of vascular smooth muscle tone. N Engl J Med 1988;319:512–3.

45. Gryglewski RJ, Botting RM, Vane JR. Mediators produced by the endothelial cell. Hypertension 1988;12:530–48.

46. James TN. De Subitaneis Mortibus. XIX. On the cause of sudden death in pheochromocytoma, with special reference to the pulmonary arteries, the cardiac conduction system, and the aggregation of platelets. Circulation 1976;54:348–56.

47. Van Vleit PD, Burchell HB, Titus JL. Focal myocarditis associated with pheochromocytoma. N Engl J Med 1966;274:1102–8.

48. James TN. Degenerative arteriopathy with pulmonary hypertension: a revised concept of so-called primary pulmonary hypertension. Henry Ford Hosp Med Bull 1961;9:271–311.

49. James TN. On the cause of syncope and sudden death in primary pulmonary hypertension. Ann Intern Med 1962;56:252–64.

50. James TN, Frame B, Schatz IJ. Pathology of cardiac conduction system in Marfan's syndrome. Arch Intern Med 1964;114:339–43.

51. James TN. Observations on the cardiovascular involvement, including the cardiac conduction system, in progressive muscular dystrophy. Am Heart J 1962;63:48–56.

52. James TN. De Subitaneis Mortibus. XXIII. Rheumatoid arthritis and ankylosing spondylitis. Circulation 1977;55:669–77.

53. Maturi MF, Greene R, Speir E, et al. Neuropeptide-Y: a peptide found in human coronary arteries constricts primarily small coronary arteries to produce myocardial ischemia in dogs. J Clin Invest 1989;83:1217–24.

54. Jasmin G, Solymoss B. Prevention of hereditary cardiomyopathy in the hamster by verapamil and other agents. Proc Soc Exp Biol Med 1975; 149:193–8.

55. Factor SM, Cho S, Scheuer J, Sonnenblick EH, Malhotra A. Prevention of hereditary cardiomyopathy in the Syrian hamster with chronic verapamil therapy. J Am Coll Cardiol 1988;12:1599–604.

56. James TN, Nadeau RA. The effect of dipyridamole on retrograde pressure in obstructed coronary arteries. J Pharmacol Exp Ther 1963;142:93–8.

57. James TN. The delivery and distribution of coronary collateral circulation. Chest 1970;58:183–203.

58. James TN. Pathology of the cardiac conduction system in hemochromatosis. N Engl J Med 1964;271:92–4.

59. Strauer BE. Die quantitative Bestimmung der Koranarreserve zur Diagnostik koranarer durch Blutungsstörungen. Der Internist 1977;18:579–87.

60. Strauer BE. Coronary hemodynamics in hypertensive heart disease: basic concepts, clinical consequences, and experimental analysis of regression of hypertensive microangiopathy. Am J Med 1988;84:45–54.

61. Cannon RO III, Watson RM, Rosing DR, Epstein SE. Efficacy of calcium channel blocker therapy for angina pectoris resulting from small-vessel coronary artery disease and abnormal vasodilator reserve. Am J Cardiol 1985;56:242–6.

62. Greenberg MA, Grose RM, Neuberger N, Silverman R, Strain JE, Cohen MV. Impaired coronary vasodilator responsiveness as a cause of lactate production during pacing-induced ischemia in patients with angina pectoris and normal coronary arteries. J Am Coll Cardiol 1987;9:743–51.

63. McGinn AL, Wilson RF, Olivari MT, Homans DC, White CW. Coronary vasodilator reserve after human orthotopic cardiac transplantation. Circulation 1988;78:1200–9.

JACC Vol. 15, No. 4
March 15, 1990:763–74

64. Nitenberg A, Foult JM, Antony I, Blanchet F, Rahali M. Coronary flow and resistance reserve in patients with chronic aortic regurgitation, angina pectoris and normal coronary arteries. J Am Coll Cardiol 1988;11:478–86.

65. Opherk D, Mall G, Zebe H, et al. Reduction of coronary reserve: a mechanism for angina pectoris in patients with arterial hypertension and normal coronary arteries. Circulation 1984;69:1–7

66. Therriault L, Lamoureux G, Cote M, Plourde G, Lemiux B. Cardiomyopathy in Friedreich's ataxia: ventriculography and myocardial imaging with thallium-201. Can J Neurol Sci 1984;11:588–91.

67. Kahan A, Nitenberg A, Foult JM, et al. Decreased coronary reserve in primary scleroderma myocardial disease. Arthritis Rheum 1985;28:637–46.

68. West BJ, Goldberger AL. Physiology in fractal dimensions. Am Sci 1987;75:354–65.